REMARKS

Claims 49-54, 56-62 and 64-65 are presently pending and under examination. Claims 49, 54, 57 and 65 have been amended. Support for the amendments can be found throughout the application as filed. In particular, support for the amendment to claim 49 can be found at, for example, Figure 1, state 14; page 6, last paragraph; page 6, lines 1-3; page 7, lines 24-26, 30; page 8, first paragraph; page 9, lines 11-17, and page 12, line 27 through page 13, line 20. The step of determining open reading frames in claim 49 has been amended to provide proper antecedent basis since the open reading frames are determined within the plurality of DNA sequences. Support for the amendment to claims 54 and 65 can be found, for example, in pending claims 53 and 54; in pending claims 57 and 61, and at, for example, page 12, line 27 through page 13, line 20, and at page 10, lines 8-11. Support for the amendment to claim 57 can be found in pending claims 49 and 57 and in the application at, for example, page 6, paragraph 5 through page 7, line 4; page 7, lines 24-26, and page 13, paragraph 3 through page 14, line 6. Accordingly, the amendments do not raise an issue of new matter and entry thereof is respectfully requested.

Applicant thanks Examiner Allen for extending a personal interview on August 21, 2006, to Applicant's representative and Dr. Christophe Schilling, during which amendments were discussed that the Examiner indicated would likely result in removal of the pending rejections. This Supplemental Response is believed to be consistent with the discussions during the interview.

Rejections Under 35 U.S.C. § 112

Claims 49-54, 56-62 and 64-65 stand rejected under 35 U.S.C. § 112, first paragraph, for lacking written description allegedly because the phrase "obtaining a DNA sequence of a genome" constitutes new matter. The Office appears to acknowledge that the specification contemplates obtaining less than the entire genome, but alleges that the claims fail to recite a term that reflects this concept in the claimed method of producing a genome specific stoichiometric matrix.

Applicant maintains that the claims as written are sufficiently supported by the application as filed. Nevertheless, to further prosecution of the subject application, claim 49 has been amended to recite a plurality of DNA sequences in a genome sufficient to produce an *in silico* representation of a microbe is obtained. As Applicant set forth in the previous response and discussed with Examiner Allen in the personal interview held August 21, 2006, the application expressly describes that less than the entire genomic sequence of an organism can be employed in the methods of the invention.

Claim 49 recites obtaining a plurality of DNA sequences. Initially, Applicant respectfully points out that "[t]o comply with written description, it is not necessary that the application describe the claimed invention in *ipsis verbis*." *Application of Edwards*, 568 F.2d 1349, 1351-52 (C.C.P.A. 1978); *see also Crown Operations Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1376, (Fed.Cir. 2002) ("the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue"); *New Railhead Mfg. L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1296 (Fed. Cir. 2002) ("[i]dentity of description is not necessary"). Because the application teaches obtaining more than one DNA sequence from a genome it provides adequate description to satisfy the written description requirements of § 112, first paragraph.

In particular, the application teaches obtaining a plurality of DNA sequence in a genome throughout its specification, claims and drawings. For example, as Applicant pointed out in the previous response, the application teaches:

> One method for obtaining the nucleotide sequences in a genome is through commercial gene databases. Many gene sequences are available on-line through a number of sites (see, for example ww.tigr.org) and can easily be downloaded from the Internet.

Response filed November 29, 2005, at page 6, paragraphs 2-3.

Apparent from the above passage is that Applicant exemplifies that one method or one process for obtaining a plurality of DNA sequences in a genome includes downloading available gene sequences from on-line databases.

Obtaining a plurality of DNA sequences in a genome also is described in the application where the application teaches that less than the entire genome of an organism can be used in construction of the claimed genome specific stoichiometric matrix. See, for example, Response filed Nov. 29, 2005, at page 6, paragraph 4 through page 8, paragraph 1. These exemplary descriptions sufficiently show that Applicant was in possession of a method of producing a genome specific stoichiometric matrix that included obtaining a plurality of DNA sequences in a genome.

The application also teaches that the claimed stoichiometric matrix can be produced from genes encoding simply those reactions determined to be present in an organism or from genomic sequences so long as homologous genes have been discovered. For example, the application describes:

> Together all of the columns of the genome specific stoichiometric matrix represent all of the chemical conversions and cellular transport processes that are determined to be present in the organism. This includes all internal fluxes and so called exchange fluxes operating within the metabolic network. Thus, the process 50 moves to a state 58 in order to formulate all of the cellular reactions together in a genome specific stoichiometric matrix. The resulting genome specific stoichiometric matrix is a fundamental representation of a genomically and biochemically defined genotype.

Application at page 9, lines 11-17 (emphasis added). The application further describes:

> Thus, the functions of nearly the entire gene complement or genotype of an organism can be determined so long as homologous genes have already been discovered.

Application at page 7, lines 24-26 (emphasis added).

The above descriptions teach that it is sufficient to include in the claimed genome specific stoichiometric matrix simply the reactants and reactions from those genes determined to be present in the organism or simply from those genes in an organism where a homologous gene has already been discovered. Together with the previous descriptions above, as well as other exemplary descriptions throughout the application, the application teaches that the claimed genome specific stoichiometric matrix can be produced by obtaining a plurality of DNA sequences in a genome that includes all, some, most, nearly all, those nucleotide sequences

available on-line in a commercial gene database, those sequences determined to be present in an organism and/or those sequences in an organism where a homologous gene has already been discovered. Accordingly, the application teaches obtaining a range of pluralities of DNA sequences in a genome.

In connection with constructing a genome specific stoichiometric matrix, the application further teaches that the claimed plurality of genes obtained to generate the matrix should be sufficient to create an *in silico* representation of a microbe. In particular, the application teaches that, when combined with linear programming, the claimed genomic stoichiometric matrix, creates an *in silico* microbial strain that is sufficient to predict genotype-phenotype relationships and/or determine the metabolic capabilities of the strain. For example, the application describes:

> Together the linear programming representation of the genome-specific stoichiometric matrix as in Equation 1 along with any general constraints placed on the fluxes in the system and any of the possible objective functions completes the formulation of the *in silico* bacterial strain. The *in silico* strain can then be used to study theoretical metabolic capabilities by simulating any number of conditions and generating flux distributions though the use of linear programming. The process 50 of formulating the *in silico* strain and simulating its behavior using linear programming techniques terminates at an end state 66.
>
> Thus, by adding or removing constraints on various fluxes in the network it is possible to (1) simulate a genetic deletion event and (2) simulate or accurately provide the network with the metabolic resources present in its in vivo environment. Using flux balance analysis it is possible to determine the affects of the removal or addition of particular genes and their associated reactions to the composition of the metabolic genotype on the range of possible metabolic phenotypes. If the removal/deletion does not allow the metabolic network to produce necessary precursors for growth, and the cell can not obtain these precursors from its environment, the deletion(s) has the potential as an antimicrobial drug target. Thus by adjusting the constraints and defining the objective function we can explore the capabilities of the metabolic genotype using linear programming to optimize the flux distribution through the metabolic network. This creates what we will refer to as an in silico bacterial strain capable of being studied and manipulated to analyze, interpret, and predict the genotype-phenotype relationship. It can be applied to assess the affects of incremental changes in the genotype or changing environmental conditions, and provide a tool for computer aided experimental design. It should be realized that other types of organisms can similarly be represented in silico and still be within the scope of the invention.

Application at page 12, line 27 through page 13, line 20 (emphasis added); *see also*, page 9, lines 18-19, 28-29; page 10, lines 8-11, 25-27; page 11, lines 6-7, 17-18; page 12, lines 4-5 (exemplifying the process of employing a genome specific stoichiometric matrix in an *in silico* representation to create an *in silico* strain that is capable of predicting genotype-phenotype relationships).

The above teachings, taken together with the teachings throughout page 9, line 11 to page 12, line 5, and elsewhere in the application, clearly exemplify that the claimed genome specific stoichiometric matrix is useful in the production of an *in silico* representation and an *in silico* strain. The *in silico* strain is useful, for example, for determining metabolic capabilities of an organism, metabolic phenotypes of an organism, affects of perturbations on such phenotypes and for predicting genotype-phenotype relationships.

Applicant has amended claim 49 to make clear that the claimed plurality of DNA sequences obtained from a genome should contain an adequate number such that the resultant stoichiometric matrix is not insufficient to work in the above useful embodiments. As Dr. Schilling explained during the personal interview August 21, 2006, one initial stoichiometric matrix of *E. coli*, for example, constructed at the time the invention was made, consisted of about 660 metabolic genes. Since the subject application was filed, additional stoichiometric matrices have been constructed that include up to about 1237 metabolic genes. Both the initial stoichiometric matrix and the subsequent versions are sufficient to be employed in an *in silico* strain that are useful as described above. These results are representative of other microbial *in silico* strains and corroborate that the claimed plurality can be only a portion of a genome because less than half of the genes encoding metabolic genes can be employed to produce useful *in silico* representations and *in silico* strains. Accordingly, claim 49 recites that the claimed plurality of DNA sequences obtained from a genome includes a number of DNA sequences in a genome sufficient to produce an *in silico* representation of a microbe. This claimed element, together with the teachings and guidance in the specification, clarifies that the claimed plurality of DNA sequences should be sufficient in number to perform it's intended use.

In light of the above remarks, Applicant submits that claim 49 is sufficiently supported by the application as originally filed and respectfully requests that this ground of rejection be withdrawn.

Claim 53 stands rejected under 35 U.S.C. § 112, first paragraph, for lacking written description allegedly because it does not require formulating the general linear programming problem representing an *in silico* strain.

As Applicant's representative and Dr. Schilling discussed during the personal interview August 21, 2006, and previously of record, claim 53 is directed to a method of producing an *in silico* representation whereas claim 54, containing the additional step of performing a flux balance analysis, is directed to use of the *in silico* strain. The production of an *in silico* representation includes combining metabolic demands and uptake rates with the claimed stoichiometric matrix (see, for example, page 9, lines 18-19, 28-29; page 10, lines 8-11, 25-27; page 11, lines 6-7, 17-18; page 12, lines 4-5 (exemplifying the process of employing a genome specific stoichiometric matrix in an *in silico* representation to create an *in silico* strain that is capable of predicting genotype-phenotype relationships)). In comparison, production of an *in silico* strain constitutes formulating the general linear programming problem which can then be used to simulate, for example, metabolic capabilities of an organism, metabolic phenotypes of an organism, affects of perturbations on such phenotypes and for predicting genotype-phenotype relationships (see, for example, page 12, line 27 through page 13, line 20). The method of solving the general linear programming problem by, for example, using flux balance analysis, constitutes simulation of the *in silico* representation or model to perform the above predictions and is set forth in claim 54.

As discussed during the interview, claim 54 has been rewritten in independent format to more particularly set forth the differences between the claimed method of producing an *in silico* representation described in the application at, for example, pages 9-12, and the claimed method of simulating a metabolic capability of an *in silico* representation as described at, for example, page 12, line 27 through page 13, line 20, and which includes solving a general linear programming problem using, for example, flux balance analysis. In light of the above remarks,

Applicant submits that claim 53 is adequately supported by the application as filed and respectfully request this ground of rejection to be withdrawn.

Claims 57-61 stand rejected for lacking written description allegedly because providing only metabolic genes in an iterative process lacks support in the specification. The Office asserts that the specification only contemplates selection of a subset of metabolic genes identified from a genome.

Claim 57 has been amended to recite that the nucleotide sequence of a metabolic gene is provided. As set forth previously and described in Applicant's previous responses, the nucleotide sequence of a metabolic gene can be obtained, for example, from known genes from an on-line gene database or by functional assignment based on nucleotide or amino acid sequence homology of an open reading frame from a genome. The metabolic genes can be identified from those genes determined to be present in a genome or from those genes in an organism where a homologous gene has already been discovered. Claim 57 includes each of these possibilities and is supported throughout the application as filed (see, for example, claim 49; page 6, paragraph 5 through page 7, line 4; page 7, lines 24-26, and page 13, paragraph 3 through page 14, line 6).

Claim 57 also recites that the steps a) and b) are repeated so as to provide a plurality of metabolic genes of the microbe sufficient to produce an *in silico* representation. As set forth previously, the claimed genome specific stoichiometric matrix is useful in the production of an *in silico* representation and an *in silico* strain which, in turn, are useful, for example, for determining metabolic capabilities of an organism, metabolic phenotypes of an organism, affects of perturbations on such phenotypes and for predicting genotype-phenotype relationships. Claim 57 recites that the repetition of steps a) and b) should be sufficient to include an adequate number of metabolic genes to achieve these useful embodiments.

Claim 49 stands rejected under 35 U.S.C. § 112, first paragraph, for lacking enablement allegedly because it requires assignment of function to every open reading frame, but that the application lacks guidance as to how to proceed if an open reading frame has little homology to genes encoding proteins of known function. Claims 49 and 57 stand similarly rejected allegedly

because one skilled in the art would not know which sequences to include or exclude in the claimed stoichiometric matrix.

Applicant maintains that the specification sufficiently enables the invention as claimed because the claims do not require assigning function to all genes in a genome. Nevertheless, claim 49 now recites obtaining a plurality of DNA sequences sufficient to produce and *in silico* representation of a microbe. Accordingly, the claimed invention expressly recites that not every open reading frame is required to have an assigned function. In light of this recited element, these grounds of rejections are moot and their withdrawal is respectfully requested.

Claims 54-55 and 64-65 stand rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because they either lack an antecedent basis or are unclear with respect to requiring production of an *in silico* representation as set forth previously under the § 112, first paragraph rejection.

As set forth above with respect to claim 53, claims 54 and 65 have been rewritten in independent format to more particularly set forth the differences between the claimed method of producing an *in silico* representation and the claimed method of simulating a metabolic capability of an *in silico* representation which includes solving a general linear programming problem using, for example, flux balance analysis. With respect to claim 64, Applicant submits that it further limits its base claim 61 because it recites one method by which the claimed uptake rates can be determined. In light of these remarks, Applicant submits that claims 54 and 65 are clear and definite. Therefore, Applicant respectfully requests withdrawal of this ground of rejection.

Rejections Under 35 U.S.C. § 102

Claims 49-51, 53-59 and 61-65 stand rejected under 35 U.S.C. § 102(b) as anticipated by Schilling et al. allegedly because the claims introduced in the continuation application constitute new matter.

While not conceding that Schilling et al. describes each and every element of the invention claimed in claims 49-51, 53-59 and 61-65, Applicant's amendments render this rejection moot. The claims as filed in the continuation application are adequately supported in

the application as of the priority date as are those claims which will be pending following entry of the amendments. Therefore, Schilling et al. does not constitute prior art and withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 52 and 60 stand rejected under 35 U.S.C. § 103(a) as obvious over Schilling et al. as applied to claims 49-51, 53-59 and 61-65 above and further because the use of BLAST would have been obvious to those skilled in the art allegedly because it is a well known search tool.

While not conceding that Schilling et al. teach or suggest the claimed invention, Applicant has set forth previously that the claims as filed in the continuation application are adequately supported in the application as are those claims which will be pending following entry of the amendments. Therefore, Schilling et al. does not constitute prior art and withdrawal of this ground of rejection is respectfully requested.

Claims 49-65 stand rejected under 35 U.S.C. § 103(a) as being obvious over Blattner et al., Pennisi, Edwards et al. (1997) and Pramanik et al. for the reasons of record. The Office asserts that Applicant's argument with respect to Pramanik et al.'s teaching away are not applicable allegedly because biochemical information with respect to *E. coli* and *H. influenzae* were known at the time of the invention.

As Applicant's representative and Dr. Schilling discussed during the personal interview on August 21, 2006, Pramanik et al. teach away from the claimed invention because Pramanik et al. teach that production of a metabolic model requires empirically determined biochemical information. In contrast, the claimed invention is directed to a genome specific stoichiometric matrix which claims the use of genomic DNA sequences to acquire metabolic functional information. Accordingly, the claimed invention does not require biochemical analysis and/or the availability or use of experimental results to generate the claimed stoichiometric matrix. The application clearly points out this teaching away when it states:

> [T]he analytical methods described by Pramanik, et al. can only be used for situations in which biochemical knowledge exists for the reactions occurring within an organism. Pramanik et al. produced a metabolic model of metabolism for *E. coli* based on biochemical information rather than genomic data since the

> metabolic genes and related reactions for *E. coli* had already been well studied and characterized. Thus, this method is inapplicable to determining a metabolic model for organisms for which little or no biochemical information on metabolic enzymes and genes is known. It can be envisioned that in the future the only information may have regarding an emerging pathogen is its genomic sequence.

Application, page 4, first paragraph (emphasis added); *see also* Response filed November 29, 2005, at page 16 (emphasis original).

Applicant further pointed out Pramanik's teaching away and inapplicability to the claimed invention when Applicant stated:

> Pramanik et al. teach away from using models that are not produced from existing biochemical information. . . . The cited combination of references fail to teach, suggest or provide a motivation to construct a stoichiometric matrix as claimed because Pramanik et al. teach away from generating a metabolic model absent actual knowledge of biochemical information. Therefore, Pramanik et al. is inapplicable in combination with a model purporting to use only genomic information such as Edwards et al. is alleged to describe

Response filed January 21, 2005, at page 17 (emphasis added); *see also* Response filed November 29, 2005, at page 16 (emphasis original).

Accordingly, Pramanik et al. is inapplicable in combination with a reference such as Edwards et al. purporting to use only genomic information. Therefore, the cited combination of references fail to teach, suggest or provide a motivation to construct a stoichiometric matrix as claimed and withdrawal of this ground of rejection is respectfully requested.

CONCLUSION

In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully requests a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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